REMARKS

Claim amendments

Claims 15, 8, 11 and 13 - 17 are rejected and are under examination. Claims 18 -21 are new. Support for the new claims is found throughout the specification. In particular, claims 18 and 19 finds support in paragraphs [0055], [0056]. Support for claim 20 is found at least in Example 3 (see paragraph [0078]). Support for claim 21 is found at least in Example 2 (see paragraph 0074]).

Rejections under 35 U.S.C. §102 and § 103

Claims 5, 8, 11 and 13-17 are rejected under 35 U.S.C. § 103 as being unpatentable over Avidano et al. in view of Grote et al. (USPN 6,670,327) and further in view of Brake et al. (USPN 4,752,576). Applicants traverse the rejection.

Avidano discloses assays for proteases obtained from patents with otorrhea resulting from tympanic membrane perforations or pressure-equalization tubes. Avidano demonstrates in vitro protease inhibition with AAT and ilomastat. However, Avidano fails to disclosse any methods of treatment.

Grote discloses the use of corticosteroids for the treatment of otitis media.

Brake teaches a method of producing AAT by recombinant methods in yeast.

However, in contrast, the claims require a method of treating an individual having otitis media and a perforated tympanic membrane comprising administering an effective, nonototoxic amound of rAAT to the middle ear by topical application to the external auditory canal.

The Applicants respectfully submit that the Examiner has failed to make out a *prima facie* case of obviousness. In order to establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, there must be some suggestion or motivation, either in the cited references themselves or in the knowledge

generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); M.P.E.P. § 2142; *Cf. Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 U.S.P.Q.2d 1161 (Fed. Cir. 1999). Second, the proposed modification of the prior art must have a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q. 1016, 1023 (Fed. Cir. 1991), *cert. denied*, 502 U.S. 856 (1991); *In re Erlich*, 22 U.S.P.Q. 1463, 1466 (Bd. Pat. App. & Int. 1992); *In re Dow Chem.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531. Third, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970); M.P.E.P. § 2142.

Here, Applicants submit that the references fail to teach or suggest all of the claim elements. Specifically, none of the references, either alone or when combined, teach or suggest a method that includes delivering to any individual, much less an individual having otitis media and a perforated tympanic membrane, an effective, nonototoxic amount of recombinant AAT to the middle ear by topical application to the external auditory canal. As noted previously, Avidano fails to teach any method of treatment. Grote does disclose treatment methods. However, there is no mention of the use of protease inhibitors including rAAT and /or ilomastat. Also, Brake fails to disclose any treatment methods.

Moreover, Applicants submit that even if all of the claim elements were present, the teachings of the references would not have provided a reasonable expectation of success in practicing the invention as claimed.

The Examiner stated that it would have been obvious to one of ordinary skill in the art to treat such patients with a combination of AAT and ilomastat "...since the combination statistically decrease protease activity". The Examiner goes on to state that the amounts of active agents to be used is "deemed obvious because once the

usefulness of the combination is know to treat a condition, it is within the skill of the artisan to determine the optimum amounts...".

Applicants traverse the rejection. Specifically, Applicants submit that the skilled artisan would not have had a reasonable expectation of success in practicing the invention *as claimed* based on the teachings of the references.

First, to reiterate, none of the references teach or suggest treating an individual with rAAT. Moreover, there is simply no teaching of treating the individual with an *effective* and *nonototoxic* amount of rAAT. As has been noted previously, in that subset of otitis media cases presenting with perforated tympanic membrane, AAT applied topically to the external canal can readily gain access to the middle ear, and thus to the site of infection and inflammation. In these cases, however, the potential toxicity of therapeutic agents is a critical clinical concern. *See, e.g.*, Roland *et al.*, "Animal ototoxicity of topical antibiotics and the relevance to clinical treatment of human subjects," *Otolaryngol. Head Neck Surg.* 130:S57-S78 (2004) and Matz *et al.*, "Ototoxicity of ototopical antibiotic drops in humans," *Otolaryngol. Head Neck Surg.* 130:S79-S82 (2004).

Indeed, even Avidano refers to the speculative nature of treating individuals. As noted in the last paragraph of p. 350 of Avidano it is noted that "[f]urther study will be required to gain a better understanding of the various types of proteases present *and to determine the clinical utility of specific protease inhibitors* in all types of chronic otitis." Thus, the primary reference calls into question the likelihood of success in using rAAT alone or in combination with other agents to treat individuals with an effective and nonototoxic amount of the agents.

To this end, Applicants remind the Examiner that the claimed invention must be considered as a whole (see MPEP 2141.02 and *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. cir. 1983)). That is, the examiner appears to have impermissibly distilled the invention to a method of treating a patient with the protease inhibitors disclosed in Avidano. However, what the Examiner has not addressed is the

uncertainty and potential ototoxicy associated with actual treatment. The claims, in contrast, require the administration of an effective and nonototoxic amount of rAAT, elements neither taught or suggested in the cited references.

As noted previously, prior to applicants' discovery, it could not be predicted whether AAT -- or inhibitors of matrix metalloproteases, notably ilomastat, or ilomastat in combination with AAT -- would prove sufficiently nonototoxic as to permit effective topical administration in the setting of a perforated tympanic membrane. Indeed, with agents drawn from a wide range of chemical classes having already, in some cases tragically, proven ototoxic,[1] the art instead clearly counsels caution in attempting topical therapy with novel agents. Given such caution, the cited art could not have provided a reasonable expectation that an effective, yet nonototoxic, dose of AAT or ilomastat could found that would permit successful treatment of otitis media in the setting of perforated tympanic membrane.

Applicants submit, therefore, that the Examiner has not established a *prima facie* case of obviousness is. *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) ("The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art.").

With failure of the *prima facie* case, the burden of production has not properly been shifted to applicants, and applicants are entitled, without more, to their claims. *In re Oetiker*, 977 F.2d 1443 (Fed. Cir. 1992).

Furthermore, applicants respectfully submit that the ototoxicity art clearly teaches away from the use of novel compounds as topical agents, a secondary indicium of the nonobviousness of applicants' topical administration of antiprotease in the clinical context of perforate tympanic membranes.

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[1] See Roland *et al.*, Table 1.

Applicants respectfully submit that the claims as now pending would have been nonobvious over the art of record, and that the rejection is in error and should be withdrawn.

CONCLUSION

Applicants submit that the present application is in condition for allowance, and respectfully request the same. If the Examiner believes that any matters remain outstanding prior to passing this case to issue, however, applicants respectfully request that the Examiner call the undersigned attorney, newly of record, for a telephonic interview.

Respectfully submitted,

HELLER EHRMAN LLP

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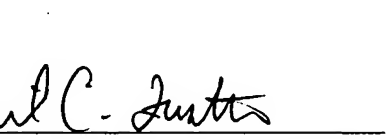

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